Factor V Leiden Is Not a Risk Factor for Myocardial Infarction Among Young Women

To the Editor:

Several large-scale studies indicate that factor V Leiden (FVL) is not associated with an increased risk of acute myocardial infarction (MI) in middle-aged or elderly populations. However, Rosendaal et al have hypothesized that FVL might increase the risk of myocardial infarction among women less than 45 years of age, particularly in the subgroup of smokers. Specifically, in a study of 84 women with premature myocardial infarction, 8 were found to carry FVL (binomial 95% confidence interval [CI], 4.2% to 17.9%). In the subgroup of smokers who carried FVL, 7 of 62 were found to be carriers of FVL (binomial 95% CI, 4.6% to 21.9%). Based on these data and on an observed control prevalence of 4.1%, the investigators reported a 32-fold increased risk of MI among the subgroup of young female smokers who carried FVL as compared with nonsmokers free of the mutation.

To directly evaluate this hypothesis, we used polymerase chain reaction techniques to determine FVL status among 36 women in the Boston area who suffered a myocardial infarction before 45 years of age and compared the prevalence of this mutation with an age-, ethnicity-, and smoking-matched group of community-based controls, as well as with the mutation rate previously reported in a large-scale population-based study of FVL in the United States. The average age of case subjects at the time of the MI was 39 years; 52% were smokers. As expected, case subjects were heavier, more likely to have a family history of premature atherothrombosis, as compared with community-based controls.

We found no evidence in these data that FVL increased the risk of MI (Table 1). Specifically, of the 36 case subjects, 1 (2.7%) was heterozygous for FVL, as compared with 3 (8.3%) of the controls (P = .3). Similarly, the prevalence of the mutation in the case group (2.7%) was not statistically different from the 4.8% prevalence rate previously reported in a large-scale population-based study of American women free of any history of coronary disease (P = .6). Moreover, in the subgroup of smokers, only 1 of 19 (5.2%) case subjects with MI was found to carry FVL.

Thus, these data do not support the hypothesis that FVL is an important risk factor for MI among young women, regardless of smoking status.

Table 1. Factor V Leiden Among Women With MI Before 45 Years of Age and Two Control Populations

<table>
<thead>
<tr>
<th></th>
<th>Case Subjects (n = 36)</th>
<th>Community-Based Controls (n = 36)</th>
<th>Population-Based Controls (n = 948)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL+</td>
<td>1 (2.7%)</td>
<td>3 (8.3%)</td>
<td>46 (4.8%)</td>
</tr>
<tr>
<td>FVL−</td>
<td>35 (97%)</td>
<td>33 (92%)</td>
<td>902 (95%)</td>
</tr>
<tr>
<td></td>
<td>P = .3</td>
<td></td>
<td>P = .6</td>
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REFERENCES

To the Editor:

Myocardial infarction is a rare but devastating disease among young women. There are few studies available, and data on genetic risk factors are especially scarce. Therefore, the attempt of Amowitz et al to evaluate our findings in a new study is commendable. However, the size of their study (36 patients) makes it difficult to interpret their findings. This becomes clear when we look at the confidence intervals of their results and our results.

We studied 84 patients and 388 controls and found (with prevalences of carriage of factor V Leiden of 10% and 4%) a relative risk of 2.4, with a 95% confidence interval of 1.0 to 5.9.1 The risk was 25- to 32-fold increased in carriers with other major risk factors, as compared with noncarriers without other major risk factors. Amowitz et al report 1 carrier among 36 patients (2.7%) and 3 among 36 controls (8.3), which leads to a relative risk of 0.3, with a confidence interval of 0.01 to 4.20. From this we conclude that these data neither support nor refute our previous, larger study. The large discrepancy in the estimates of the carrier prevalence among controls (8.3% among 36 controls and 4.8% among 948 controls) illustrates the instability of estimates based on such small samples.

Recently, we have shown that another common prothrombotic mutation, the 20210 G to A variant of the protrombin gene, which is present in 2% to 4% of whites,2 increases the risk of myocardial infarction fourfold in young women3 and that the combination of the mutation with a major cardiovascular risk factor leads to a 43-fold increased risk (compared with women with neither). A further analogy may be found in a large study among (mainly middle-aged) men with myocardial infarction (560 patients and 646 controls), to which we found mildly elevated risks associated with both factor V Leiden and protrombin 20210A and also more pronounced risks in the presence of other risk factors.4 We feel that the magnitude of these risks estimates and the analogies between the two abnormalities and the sexes indicate the associations to be real. Nevertheless, we too are interested in extending these findings, for which larger population-based studies are under way in Seattle and Leiden.

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REFERENCES

GATA-1 Transcription Factor Transactivates the Promoter for CCR5, a Coreceptor for Human Immunodeficiency Virus Type 1 Entry

To the Editor:

Human immunodeficiency virus type 1 (HIV-1) is determined by binding of the viral envelope to the CD4 molecule as well as to a coreceptor such as CCR5 or CXCR4.1 Expression of CCR5 is apparently restricted to certain cell types (ie, lymphocytes, monocyte/macrophages, or CD34+ progenitor cells),2,4 which are susceptible to macrophage (M)-tropic (or R5) strains of HIV-1. Because most primary isolates of HIV-1 use CCR5 to enter cells and levels of CCR5 expression correlate well with the infectability with M-tropic HIV-1 in vitro,2 it is important to delineate the cellular and molecular mechanisms whereby expression of CCR5 is regulated. The present study demonstrates that the transcription factor GATA-1 can upregulate CCR5 promoter activity.

The CCR5 promoter region contains at least three GATA-binding elements (Fig 1A). We have previously identified one of those elements as a GATA-1 binding site1 and have designated it as GATA#1. Characterization of the further upstream region demonstrated another GATA binding site (GATA#2) between −734 and −739 relative to the transcription start site (TSS; data not shown). Further characterization of promoter activity in transient expression assays. Plasmid pGL-CCR5(WT) contains the CCR5 promoter region between −770 and +61 relative to the TSS, followed by the luciferase gene, and plasmids pGL-CCR5ΔGATA#1, pGL-CCR5ΔGATA#2, pGL-CCR5ΔGATA#3, and pGL-CCR5ΔGATA#1+2+3 have mutations on these GATA-binding sites individually or in combination (see Fig 1A for mutated nucleotides). The indicated CCR5 promoter-luciferase reporter construct was cotransfected with either a GATA-1 expression vector (pMT-GATA1; kindly provided by S.H. Orkin, Harvard University, Boston, MA) or its parent plasmid (pMT2T) into PM1 cells (CCR5-positive,2,4 CD4+ T-lymphoid cell line) or THP-1 cells (CCR5-positive,2 monocyted cell line). Expression of GATA1, but not GATA-2 or GATA-3 (data not shown), upregulated CCR5 promoter activity up to 15-fold; however, mutation on GATA#1 markedly reduced GATA-1-mediated transactivation of the CCR5 promoter (Fig 2). Whereas mutation on GATA#2 or
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